Targeting metabotropic glutamate receptors (mGluRs) in Parkinson's disease

Marianne Amalric

The interplay between dopamine and glutamate in the basal ganglia regulate critical aspects of motor and cognitive behavior. Metabotropic glutamate (mGlu) receptors are key modulators of glutamatergic dysfunction in Parkinson's disease (PD). Preclinical evidence demonstrate that group I mGlu receptor antagonism and groups II and III mGlu receptor activation improve motor symptomatology of PD and decrease L-DOPA-induced dyskinesia by regulating excitatory and inhibitory transmission in the basal ganglia. Emotional and cognitive deficits are also observed in PD. Treatment of these symptoms is challenging and underscore the need for novel effective and well tolerated pharmacological treatments. This article will thus review the currently available knowledge regarding the therapeutic potential of targeting mGlu receptors to restore motor and nonmotor symptoms of PD.

Addresses
Aix-Marseille University, CNRS UMR 7291, Laboratoire de Neurosciences Cognitives (LNC), FR3C 3512, 13331 Marseille, France

Corresponding author: Amalric, Marianne
(Marianne.amalric@univ-amu.fr)

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The basal ganglia (BG) are a network of subcortical structures involved in the regulation of voluntary movements and cognitive processes. Dopamine (DA) and glutamate systems in the BG are oppositely regulated and play a crucial role in the pathophysiology of these structures. The degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) in Parkinson's disease (PD) results in excessive activity of glutamatergic neurons of the subthalamic nucleus (STN) projecting to BG output structures, and this is believed to contribute to the motor symptoms of PD (Figure 1) [1]. Beside the classical motor symptoms (akinesia, bradykinesia, rigidity and tremor) PD patients experience a range of neuropsychiatric symptoms, including depression, anxiety, cognitive disturbances and psychosis [2]. The classical palliative therapy of PD with L-3,4-dihydroxyphenylalanine (L-DOPA) provides motor benefits, has limited beneficial action on nonmotor symptoms and leads to abnormal involuntary movements, termed L-DOPA-induced dyskinesias (LID), with a frequency of 30–80% after 5–10 years of treatment. Therefore, novel pharmacological treatments that specifically target this excessive glutamatergic activity may prove to be clinically beneficial. The first attempts to pharmacologically oppose glutamate hyperactivity have focused on antagonists at ionotropic glutamate receptors (iGlu). They have good antiparkinsonian properties in preclinical studies, but may produce debilitating side effects in humans that reduce their development in clinic. Because of their modulatory role on glutamatergic transmission, metabotropic glutamate (mGlu) receptors provide an alternative way to regulate increased glutamatergic transmission in the BG.

The mGluRs are a family of eight G-protein-coupled receptors, divided into three groups (Groups I, II and III) according to sequence homology and ligand-binding profile (for review [3–5]). They are coupled with different G proteins and mediate slow modulatory effects on post-synaptic neurons via either pre-synaptic or post-synaptic mechanisms [6]. They are widely expressed in the BG where they regulate synaptic transmission and plasticity in physiological and pathological conditions [7–9]. In patients with PD, degeneration of dopamine nigral neurons within the SNc results in loss of dopaminergic modulation of the balance between inhibition and excitation of the major output nuclei of the basal ganglia (Figure 1). This is achieved via direct and indirect inhibitory projections (GABAergic) from the striatum (caudate nucleus/putamen) to the globus pallidus internal (GPi)/substantia nigra pars reticulate (SNr) and excitatory projections (glutamatergic) from the STN to the substantia nigra pars compacta (SNc) and GPi/SNr. The pre-synaptic and post-synaptic localization of mGlu receptor subtypes in the BG are illustrated in Figure 1. In this review, we will discuss their function and implication in the expression of the characteristic motor symptoms of PD (mainly akinesia, a failure to initiate movements) and the development of LID. Their potential as novel therapeutic targets for cognitive and neuropsychiatric symptoms in PD will then be reviewed in view of the most recent clinical studies on schizophrenia and depression.

Figure 1
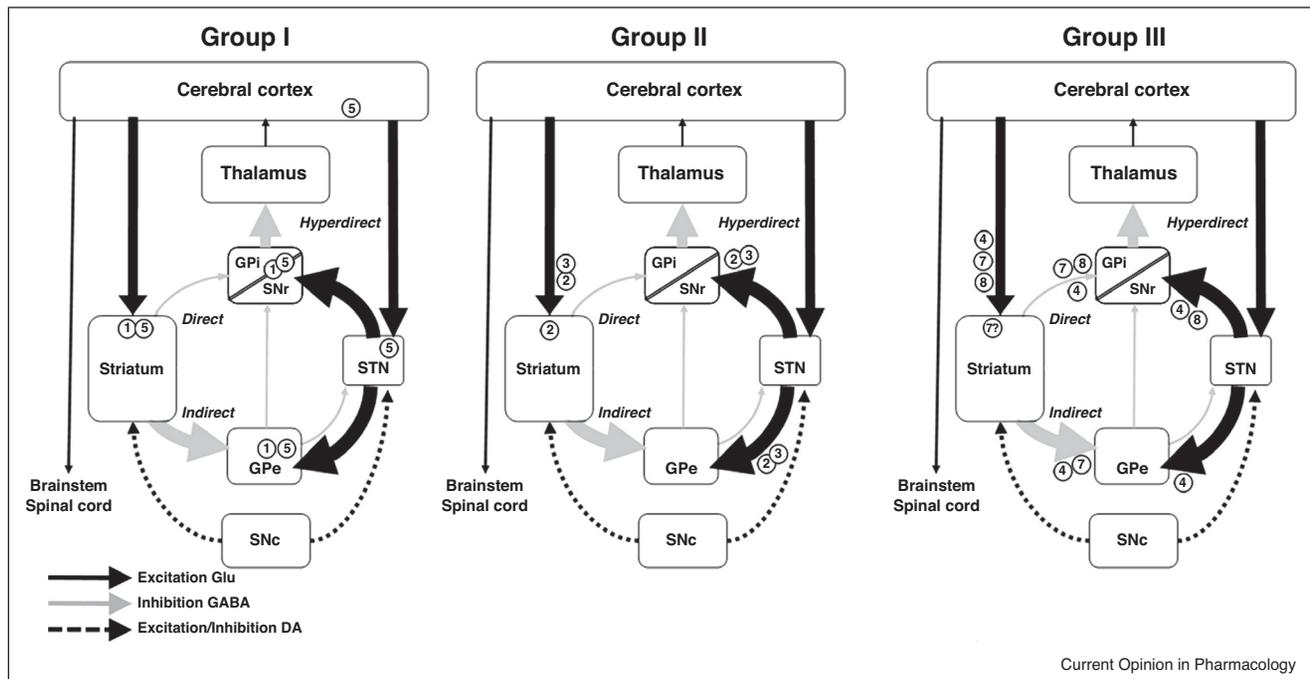
Localization of Group I, II and III mGlu receptor subtypes in the Basal Ganglia circuitry in PD state. Group I (mGlu1-5, circled numbers) mGlu receptors are mainly located postsynaptically within each structure of the BG. Group II (mGlu2-3) and Group III (mGlu4-8, mGlu6 receptors are only expressed in the retina) mGlu receptors are positioned along the arrows to represent their presynaptic localization, as indicated by immunohistochemical studies (for review [7,14]). MGlu2 and 3 receptors are mainly co-localized. The classical view of the pathophysiological model of the basal ganglia (today revisited [64]) predicts that the loss of dopamine neurons (dashed lines) of the substantia nigra pars compacta (SNc) in Parkinson's disease leads to opposite effects on the two main striatal efferent neurons, which project respectively to the globus pallidus pars externa (GPe) ('indirect' pathway) or the globus pallidus pars internal (GPi)/SNr ('direct' pathway). Increased activity of striatal GABA neurons projecting to the GPe leads to the over-inhibition of the GP, which in turn results in the disinhibition of the STN. Hyperactivity of the STN, leading to excessive inhibitory output from the GPi and SNr to the thalamus, thereby reducing thalamocortical input, is considered as the pathophysiological hallmark of Parkinson's disease.

Implication of mGlu receptors for motor symptoms of Parkinson's disease and LID
Group I mGlu receptor modulation

Support for a role of group I mGlu (mGlu1 and mGlu5) receptors in the pathogenesis of PD steams from early studies showing that mGluR5 antagonists ameliorate the motor alterations in animal model of parkinsonism [7,10,11] and are neuroprotective against MPTP neurotoxicity in animals [12,13]. They are heavily distributed postsynaptically in key basal ganglia nuclei, including the striatum, the GP external segment (GPe), the SNr and the STN (Figure 1), where they mediate excitatory effects. MGlu1 receptors are expressed in the GP and SNr and at a lower level in the striatum, where they are mainly coexpressed with mGlu5 receptors [7,14–17]. However, because of this co-expression and the few group I antagonists with no activity at mGlu5 receptors, mGlu1 receptor antagonism in animal models of PD has not been thoroughly examined. In contrast, negative allosteric modulators (NAMs), which exhibit non-competitive inhibition of mGlu5 receptors, such as MPEP (2-methyl-6-(phenylethenyl)-pyridine) and

MTEP (3-(2-methyl-1,3-thiazol-4-yl(ethynyl)pyridine)), are highly effective in relieving motor symptoms and LIDs in a variety of rodent and nonhuman primate models of PD (for review [8,18•]). Interestingly, a chronic administration rather than acute treatment with MPEP reverses akinesia in a reaction time task in partially dopamine-depleted rats, mimicking the early stages of PD [19–21]. Further studies indicate that mGlu5 receptor blockade normalizes the hyperactive subthalamic nucleus and the cortical input onto striatopallidal neurons (i.e. the 'indirect' pathway) [22]. These antiparkinsonian-like effects raise potential interesting clinical development for motor symptomatic improvement in early PD. Despite these positive findings on motor symptoms, the major breakthrough in the field of mGlu receptors research in PD was found in the management of LID [18•,23••]. Increased postsynaptic mGlu5 receptor density and specific striatal binding with selective mGlu5-receptor ligand are observed in MPTP-lesioned macaques with dyskinesia [24,25] and in postmortem brains of parkinsonian patients with dyskinesia [26]. Further evidence for anti-dyskinetic efficacy of mGluR5

antagonists in LID comes from preclinical studies in 6-OHDA-lesioned rats and MPTP monkeys [18•,23••]. This led to several clinical (phase II and III) studies which evaluated two mGlu5 receptor NAMs mavoglurant and dipraglurant in PD patients. They showed potential to reduce LID in PD without reducing efficacy of anti-parkinsonian therapy [23••]. Adverse effects including dizziness and hallucinations were reported, however, which require characterization before further clinical development. A potential role for CNS structures outside the BG, such as the lateral habenula and hippocampus, in the expression of LIDs has recently been emphasized [27]. Inhibition of glutamate activity at mGlu receptors located in these areas may prove to be a novel target to reduce LIDS [28].

Group II mGlu receptor modulation

Group II mGlu receptors (mGlu2 and 3) may also represent a drug target of potential interest for the treatment of parkinsonian motor symptoms, as selective agonists of mGlu2 and 3 receptors potently decrease excitatory transmission at corticostriatal synapses via a presynaptic mechanism (Figure 1) [29,30•]. In the context of motor symptomatology, however, the modulation of these receptors does not provide significant benefit in animal models of PD. The selective mGlu2/3 receptor agonist LY379268 tended to reduce rotarod performance in animal models of the disease [31] but failed to reverse akinesia in 6-OHDA-lesioned rats and even worsen motor symptoms [32]. In contrast to mGlu5 receptors, the expression of mGluR2/3 in the basal ganglia of MPTP monkeys does not change with L-DOPA treatment and dyskinesia development [33]. LY379268 had no beneficial effect on LIDs [31]. These data support the view that group II mGluRs do not play a significant role in LID. The recent development of subtype 2 or 3 selective agonists may help to resolve this issue. Based on recent studies showing a clear benefit of modulating group II mGlu receptors in major depression disorder, anxiety and schizophrenia, Group II mGlu receptor agonists might be more appropriate in the treatment of neuropsychiatric symptoms of PD.

Group III mGlu receptor modulation

Group III (mGlu4, 7 and 8 receptors) are expressed at glutamatergic and GABAergic nerve terminals in most BG nuclei (Figure 1), while mGlu6 receptors are exclusively localized in the retina. MGlu4 in particular is expressed at a GABAergic and glutamatergic synapses in the indirect pathway of BG circuitry (in the GPe) overactive in PD [34]. Activation of mGlu4 at this location significantly reduces synaptic transmission at striatopallidal GABAergic synapses and subthalamopallidal glutamatergic synapses thus restoring balance within the BG motor circuit. In the recent years, interest in drug development has focused on selectively activating mGlu4 using positive allosteric modulators (PAMs). These positive allosteric modulators are non-competitive because they bind mGlu4 receptors at a different site than the binding receptor site and potentiate the mGlu4 receptor response to endogenous glutamate. They generally have good selectivity and good brain penetration [18,35]. However, mGlu4 PAMs have produced little or no benefit on motor symptoms in rat PD models, unless co-administered with L-DOPA or adenosine A2a receptor antagonists [36–38], possibly due to a lack of action at GABAergic synapses in the GP [39]. On the other hand, orthosteric agonists (L-AP4, LSP1-2111) act directly on the glutamate binding site, have good solubility and are active after systemic administration [40]. When directly injected into key overactive structures of the BG in PD conditions, orthosteric agonists highlighted the GPe, the excitatory subthalamonigral and corticostriatal pathways as critical sites for their antiparkinsonian action [7,41–44] (for review see [45]), whereas their intranigral administration worsen parkinsonian-like akinesia [44]. Selective activation of mGlu 8 receptors may account for these deleterious effects as a novel orthosteric agonist (LSP4-2022) with a preferential affinity on mGlu4 over mGlu8 receptors potently reverses akinesia in a pharmacological PD model [46]. Only modest improvement of motor symptoms is achieved by the activation of mGlu7 receptor using the PAM (N,N′-dibenzhydrylethane-1,2-diamine dihydrochloride) (AMN082) [47,48]. Because of their high solubility and effectiveness after systemic administration, novel selective group III orthosteric agonists acting at mGlu4 subtypes may offer appropriate motor symptomatic benefit in the treatment of PD [40]. MGlu4 PAMs (VU0364770) and mGlu7 receptors have good efficacy in animal models of LIDs, presumably by reducing glutamate transmission at the corticostriatal pathway [37,38,49]. Studies testing systemic administration of a new mGlu4 PAM, Lu AF21934, further demonstrated a reduction of the development of LIDs but not its severity [38].

mGlu receptors potential implication in neuropsychiatric symptoms of Parkinson's disease

Extensive neuropsychiatric features are now increasingly recognized in PD. These nonmotor symptoms may appear at early stages of the disease prior to the onset of motor deficits and represent early markers of the disease progression [2]. Impaired cognitive function, anxiety and depression have recently been found in rodent models of PD after moderate DA depletion in the striatum [49–52]. These early nonmotor symptoms may involve in addition structures outside the BG, such as the hippocampus, prefrontal cortex and nondopaminergic neuromodulatory systems such as the serotonergic ascending pathways. The therapeutic potential of mGlu receptor activation on PD psychiatric and cognitive functions has not been investigated so far, however, extensive evidence support mGlu receptor modulation for the

treatment of schizophrenia, major depression and cognitive deficits [8,30•,53,54]. Studies using mGlu5 or mGlu2 knockout mice display sensorimotor gating deficits while mGlu7 and mGlu8 knockout mice express impaired cognitive function, anxiety-like phenotype, strengthening the involvement of these mGlu receptor subtypes in the pathophysiology of schizophrenia and cognitive dysfunction [8]. Because of the opposing action of the glutamatergic and DAergic system in the striatum and in the frontal cortical areas, mGlu receptors, particularly mGlu5 and mGlu2/3 receptors positive modulation may represent novel therapeutic strategies for treating mood and neuropsychiatric disorders. Recent studies support the impact of potentiating mGlu5 receptor function in learning and memory tasks [55-57]. Activation of mGlu5 receptor indirectly enhances NMDA receptor function in brain regions (BG, cortex and hippocampus) involved in positive symptoms and cognitive deficits and PAMs are active in various rodent models [58••,59]. However, a recent study reveals that selective mGlu5 receptor PAMs having antipsychotic activity may also induce neurotoxicity in brain regions with high mGlu5 expression such as the auditory cortex and hippocampus [60••]. Further investigation to elucidate the mechanisms involved in mGlu5 PAM-induced cell death is crucially needed and the development of selective mGlu5 orthosteric agonist may be a useful alternative. Another target would be to inhibit glutamate release at key synapses with both mGlu2/3 specific ligands and mGlu7 agonist as they are known to provide enhancement of cognitive functions and possess anxiolytic properties [55,61–63]. This raises the paradoxical proposition of decreasing overactive glutamate pathways in the BG to reduce motor impairment and LID in PD, while enhancing glutamate function in the frontal cortex and the hypothalamus to improve cognition, reduce psychotic episode, anxiety and depression that occur in high proportion of patients during the course of the disease.

Conclusions

The nigral dopamine cell loss in Parkinson's disease is associated with increased glutamatergic transmission at corticostriatal and subthalamofugal pathways in the BG circuitry. The dense expression of mGlu receptors with a specific distribution of the different subtypes in key structures of the BG and the modulatory nature of their transmission provide an alternative therapeutic target to the classical L-DOPA therapy for the treatment of PD. From the collection of preclinical studies summarized here, it is clear that a reduction in the excitatory drive through antagonism of mGlu5 receptors may offer significant benefit in animal models of PD. In recent years, intense effort has been concentrated in the synthesis and characterization of novel, more selective drugs acting on selective subtypes of mGluRs now tested in clinic for the treatment of LID. However, novel therapeutic approaches may benefit from the combined selective targeting of multiple mGlu receptors, such as mixed mGlu5 receptor antagonist and mGlu4 agonist to potentiate their effects. The main challenge for research in the field of PD is to better characterize the neuropsychiatric, cognitive decline and mood disorders afflicting 40–70% of PD patients. Taking advantage of the advanced research in the pathophysiology of other diseases with similar nonmotor symptoms, such as schizophrenia, the development of novel mGlu receptor modulation may help to resolve this issue.

Conflict of interest statement

Nothing declared.

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